RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 5 OF 5 CA COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 136:99884 CA
TITLE: BNIP3 protein inducing necrosis-like cell death independent of caspases and Apaf-1/cytochrome c pathway
INVENTOR(S): Kohn, Kenneth I.; Greenberg, Arnold H.
PATENT ASSIGNEE(S): University of Manitoba, Can.
SOURCE: PCT Int. Appl., 82 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2002002743 | A2 | 20020110 | WO 2001-US21043 | 20010629 <-- |
| WO 2002002743 | A3 | 20020516 | | |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG | | | | |
| CA 2413250 | AA | 20020110 | CA 2001-2413250 | 20010629 <-- |
| AU 2001071767 | A5 | 20020114 | AU 2001-71767 | 20010629 <-- |
| EP 1299127 | A2 | 20030409 | EP 2001-950808 | 20010629 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR | | | | |
| US 2003203867 | A1 | 20031030 | US 2002-290461 | 20021108 |

PRIORITY APPLN. INFO.:

| | | |
|---|---|---|
| US 2000-215643P | P | 20000630 |
| US 2000-219554P | P | 20000720 |
| WO 2001-US21043 | W | 20010629 |
| US 2001-348135P | P | 20011109 |
| US 2001-344196P | P | 20011228 |

AB The present invention discloses that **BNIP3** (Bcl2/adenovirus EIB 19kD-interacting protein 3) protein induces necrosis-like cell death independent of Apaf-1, caspases activation, and mitochondrial cytochrome c release. The invention also provides the isolated and purified **BNIP3** protein and a method for inducing cell death by creating a transgene overexpressing **BNIP3** protein in the transfecting cells, such as cardiac **myocytes**. In particular, the **BNIP3** overexpression initiates a cell death pathway including activation of the cell death by protein integration into the outer mitochondrial membrane, opening of the permeability transition (PT) pore which is independent of caspases, Apaf-1 and cytochrome c release, and manifestation of the mitochondrial dysfunction, plasma membrane damage and the morphol. of necrosis. The invention also provides vectors encoding **BNIP3** or its **mutant** form DN NIP with promoters for uses in gene therapy, and methods of treating diseases by inducing or inhibiting necrosis.

=> s webster, k?/au
L7 1942 WEBSTER, K?/AU

=> d his

(FILE 'HOME' ENTERED AT 13:41:02 ON 11 MAY 2006)

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     FILE 'MEDLINE, BIOSIS, CA, EMBASE, SCISEARCH' ENTERED AT 13:41:08 ON 11
     MAY 2006
L1           812 S (NIP3 OR BNIP3)
L2       3223884 S MYOC? OR MUSCL?
L3            63 S L2 (P) L1
L4            19 S L3 AND (MUTA? OR (DOMINA? (N) NEGAT?))
L5             9 DUP REM L4 (10 DUPLICATES REMOVED)
L6             5 S L5 AND PY<=2002
L7          1942 S WEBSTER, K?/AU

=> s l7 and l1
L8            23 L7 AND L1

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PROCESSING COMPLETED FOR L8
L9            11 DUP REM L8 (12 DUPLICATES REMOVED)

=> s l9 and py<=2002
   1 FILES SEARCHED...
L10            5 L9 AND PY<=2002

=> s l10 not l6
L11            4 L10 NOT L6

=> d l11 ibib abs 1-4

L11  ANSWER 1 OF 4  BIOSIS  COPYRIGHT (c) 2006 The Thomson Corporation  on STN
ACCESSION NUMBER:   2003:80078  BIOSIS
DOCUMENT NUMBER:    PREV200300080078
TITLE:              BNIP3 activates a mitochondrial death pathway in
                    cardiac muscle subjected to hypoxia and acidosis.
AUTHOR(S):          Kubasiak, Lori A. [Reprint Author]; Frazier, Donna P.
                    [Reprint Author]; Li, Huifang [Reprint Author]; Graham,
                    Regina M. [Reprint Author]; Bishopric, Nanette H. [Reprint
                    Author]; Webster, Keith A. [Reprint Author]
CORPORATE SOURCE:   University of Miami, Miami, FL, USA
SOURCE:             Circulation, (November 5 2002) Vol. 106, No. 19
                    Supplement, pp. II-108. print.
                    Meeting Info.: Abstracts from Scientific Sessions. Chicago,
                    IL, USA. November 17-20, 2002. American Heart Association.
                    ISSN: 0009-7322 (ISSN print).
DOCUMENT TYPE:      Conference; (Meeting)
                    Conference; Abstract; (Meeting Abstract)
LANGUAGE:           English
ENTRY DATE:         Entered STN: 6 Feb 2003
                    Last Updated on STN: 6 Feb 2003

L11  ANSWER 2 OF 4  BIOSIS  COPYRIGHT (c) 2006 The Thomson Corporation  on STN
ACCESSION NUMBER:   2002:264007  BIOSIS
DOCUMENT NUMBER:    PREV200200264007
TITLE:              Hypoxia-acidosis activated apoptosis of cardiac myocytes is
                    mediated by MPTP opening and BNIP3 activation.
AUTHOR(S):          Kubasiak, Lori [Reprint author]; Discher, Daryl; Bishopric,
                    Nanette H.; Webster, Keith A.
CORPORATE SOURCE:   Univ of Miami, Miami, FL, USA
SOURCE:             Circulation, (October 23, 2001) Vol. 104, No. 17
                    Supplement, pp. II.203. print.
                    Meeting Info.: Scientific Sessions 2001 of the American
                    Heart Association. Anaheim, California, USA. November
                    11-14, 2001. American Heart Association.
                    CODEN: CIRCAZ. ISSN: 0009-7322.
DOCUMENT TYPE:      Conference; (Meeting)
                    Conference; Abstract; (Meeting Abstract)
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LANGUAGE: English
ENTRY DATE: Entered STN: 1 May 2002
Last Updated on STN: 1 May 2002

L11 ANSWER 3 OF 4 SCISEARCH COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 2003:621636 SCISEARCH
THE GENUINE ARTICLE: 613QJ
TITLE: **BNIP3** activates a mitochondrial death pathway in cardiac muscle subjected to hypoxia and acidosis
AUTHOR: Kubasiak L A (Reprint); Frazier D P; Li H F; Graham R M; Bishopric N H; **Webster K A**
CORPORATE SOURCE: Univ Miami, Miami, FL 33152 USA
COUNTRY OF AUTHOR: USA
SOURCE: CIRCULATION, (**5 NOV 2002**) Vol. 106, No. 19, Supp. [S], pp. 108-108. MA 544.
ISSN: 0009-7322.
PUBLISHER: LIPPINCOTT WILLIAMS & WILKINS, 530 WALNUT ST, PHILADELPHIA, PA 19106-3621 USA.
DOCUMENT TYPE: Conference; Journal
LANGUAGE: English
REFERENCE COUNT: 0
ENTRY DATE: Entered STN: 8 Aug 2003
Last Updated on STN: 8 Aug 2003

L11 ANSWER 4 OF 4 SCISEARCH COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 2001:936373 SCISEARCH
THE GENUINE ARTICLE: 487UW
TITLE: Hypoxia-acidosis activated apoptosis of cardiac myocytes is mediated by MPTP opening and **BNIP3** activation
AUTHOR: Kubasiak L (Reprint); Discher D; Bishopric N H; **Webster K A**
CORPORATE SOURCE: Univ Miami, Miami, FL 33152 USA; Univ Miami, Sch Med, Miami, FL USA
COUNTRY OF AUTHOR: USA
SOURCE: CIRCULATION, (**23 OCT 2001**) Vol. 104, No. 17, Supp. [S], pp. 203-203. MA 976.
ISSN: 0009-7322.
PUBLISHER: LIPPINCOTT WILLIAMS & WILKINS, 530 WALNUT ST, PHILADELPHIA, PA 19106-3621 USA.
DOCUMENT TYPE: Conference; Journal
LANGUAGE: English
REFERENCE COUNT: 0
ENTRY DATE: Entered STN: 7 Dec 2001
Last Updated on STN: 7 Dec 2001

=> d his

(FILE 'HOME' ENTERED AT 13:41:02 ON 11 MAY 2006)

FILE 'MEDLINE, BIOSIS, CA, EMBASE, SCISEARCH' ENTERED AT 13:41:08 ON 11 MAY 2006

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L1          812 S (NIP3 OR BNIP3)
L2      3223884 S MYOC? OR MUSCL?
L3           63 S L2 (P) L1
L4           19 S L3 AND (MUTA? OR (DOMINA? (N) NEGAT?))
L5            9 DUP REM L4 (10 DUPLICATES REMOVED)
L6            5 S L5 AND PY<=2002
L7         1942 S WEBSTER, K?/AU
L8           23 S L7 AND L1
L9           11 DUP REM L8 (12 DUPLICATES REMOVED)
L10           5 S L9 AND PY<=2002
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L11 4 S L10 NOT L6

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Enter choice (y/N):
Enter new loginid (or press [Enter] for ssspta1635jxs):
Enter new password:

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LOGINID:ssspta1635jxs

PASSWORD:
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 NEWS  1          Web Page URLs for STN Seminar Schedule - N. America
 NEWS  2          "Ask CAS" for self-help around the clock
 NEWS  3  JAN 17  Pre-1988 INPI data added to MARPAT
 NEWS  4  FEB 21  STN AnaVist, Version 1.1, lets you share your STN AnaVist
                  visualization results
 NEWS  5  FEB 22  The IPC thesaurus added to additional patent databases on STN
 NEWS  6  FEB 22  Updates in EPFULL; IPC 8 enhancements added
 NEWS  7  FEB 27  New STN AnaVist pricing effective March 1, 2006
 NEWS  8  MAR 03  Updates in PATDPA; addition of IPC 8 data without attributes
 NEWS  9  MAR 08  X.25 communication option no longer available after June 2006
 NEWS 10  MAR 22  EMBASE is now updated on a daily basis
 NEWS 11  APR 03  New IPC 8 fields and IPC thesaurus added to PATDPAFULL
 NEWS 12  APR 03  Bibliographic data updates resume; new IPC 8 fields and IPC
                  thesaurus added in PCTFULL
 NEWS 13  APR 04  STN AnaVist $500 visualization usage credit offered
 NEWS 14  APR 12  LINSPEC, learning database for INSPEC, reloaded and enhanced
 NEWS 15  APR 12  Improved structure highlighting in FQHIT and QHIT display
                  in MARPAT
 NEWS 16  APR 12  Derwent World Patents Index to be reloaded and enhanced during
                  second quarter; strategies may be affected
 NEWS 17  MAY 10  CA/CAplus enhanced with 1900-1906 U.S. patent records
 NEWS 18  MAY 11  KOREAPAT updates resume

 NEWS EXPRESS  FEBRUARY 15 CURRENT VERSION FOR WINDOWS IS V8.01a,
               CURRENT MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP),
               AND CURRENT DISCOVER FILE IS DATED 19 DECEMBER 2005.
               V8.0 AND V8.01 USERS CAN OBTAIN THE UPGRADE TO V8.01a AT
               http://download.cas.org/express/v8.0-Discover/
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=> FIL MEDLINE BIOSIS CA EMBASE SCISEARCH

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|---|---|---|
| FULL ESTIMATED COST | 0.21 | 0.21 |

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FILE 'SCISEARCH' ENTERED AT 13:41:08 ON 11 MAY 2006
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=> s (nip3 or bnip3)
L1 812 (NIP3 OR BNIP3)

=> s myoc? or muscl?
L2 3223884 MYOC? OR MUSCL?

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=> s l2 (p) l1
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=> s l3 and (muta? or (domina? (n) negat?))
L4          19 L3 AND (MUTA? OR (DOMINA? (N) NEGAT?))

=> dup rem l4
PROCESSING COMPLETED FOR L4
L5           9 DUP REM L4 (10 DUPLICATES REMOVED)

=> s l5 and Py<=2002
   1 FILES SEARCHED...
L6           5 L5 AND PY<=2002

=> d l6 ibib abs 1-5

L6   ANSWER 1 OF 5     MEDLINE on STN
ACCESSION NUMBER:   2002498687     MEDLINE
DOCUMENT NUMBER:    PubMed ID: 12226479
TITLE:              Hypoxia and acidosis activate cardiac myocyte
                    death through the Bcl-2 family protein BNIP3.
AUTHOR:             Kubasiak Lori A; Hernandez Olga M; Bishopric Nanette H;
                    Webster Keith A
CORPORATE SOURCE:   Department of Molecular and Cellular Pharmacology,
                    University of Miami Medical Center, Miami, FL 33136, USA.
CONTRACT NUMBER:    HL44578 (NHLBI)
                    HL69812 (NHLBI)
SOURCE:             Proceedings of the National Academy of Sciences of the
                    United States of America, (2002 Oct 1) Vol. 99,
                    No. 20, pp. 12825-30.  Electronic Publication: 2002-09-11.
                    Journal code: 7505876. ISSN: 0027-8424.
PUB. COUNTRY:       United States
DOCUMENT TYPE:      Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:           English
FILE SEGMENT:       Priority Journals
ENTRY MONTH:        200211
ENTRY DATE:         Entered STN: 3 Oct 2002
                    Last Updated on STN: 5 Jan 2003
                    Entered Medline: 13 Nov 2002
AB   Coronary artery disease leads to injury and loss of myocardial
     tissue by deprivation of blood flow (ischemia) and is a major underlying
     cause of heart failure.  Prolonged ischemia causes necrosis and apoptosis
     of cardiac myocytes and vascular cells; however, the mechanisms
     of ischemia-mediated cell death are poorly understood.  Ischemia is
     associated with both hypoxia and acidosis due to increased glycolysis and
     lactic acid production.  We recently reported that hypoxia does not induce
     cardiac myocyte apoptosis in the absence of acidosis.  We now
     report that hypoxia-acidosis-associated cell death is mediated by
     BNIP3, a member of the Bcl-2 family of apoptosis-regulating
     proteins.  Chronic hypoxia induced the expression and accumulation of
     BNIP3 mRNA and protein in cardiac myocytes, but acidosis
     was required to activate the death pathway.  Acidosis stabilized
     BNIP3 protein and increased the association with mitochondria.
     Cell death by hypoxia-acidosis was blocked by pretreatment with antisense
     BNIP3 oligonucleotides.  The pathway included extensive DNA
     fragmentation and opening of the mitochondrial permeability transition
     pore, but no apparent caspase activation.  Overexpression of wild-type
     BNIP3, but not a translocation-defective mutant,
     activated cardiac myocyte death only when the myocytes
     were acidic.  This pathway may figure significantly in muscle
     loss during myocardial ischemia.

L6   ANSWER 2 OF 5     MEDLINE on STN
ACCESSION NUMBER:   2002415349     MEDLINE
```

DOCUMENT NUMBER: PubMed ID: 12169648
TITLE: Inducible expression of **BNIP3** provokes mitochondrial defects and hypoxia-mediated cell death of ventricular **myocytes**.
AUTHOR: Regula Kelly M; Ens Karen; Kirshenbaum Lorrie A
CORPORATE SOURCE: Institute of Cardiovascular Sciences, St Boniface General Hospital Research Centre, and the Department of Physiology, Faculty of Medicine, University of Manitoba, Winnipeg, Manitoba, Canada.
SOURCE: Circulation research, **(2002 Aug 9)** Vol. 91, No. 3, pp. 226-31.
Journal code: 0047103. E-ISSN: 1524-4571.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200208
ENTRY DATE: Entered STN: 10 Aug 2002
Last Updated on STN: 23 Aug 2002
Entered Medline: 22 Aug 2002

AB In this study, we provide evidence for the operation of **BNIP3** as a key regulator of mitochondrial function and cell death of ventricular **myocytes** during hypoxia. In contrast to normoxic cells, a 5.6-fold increase (P<0.05) in **myocyte** death was observed in cells subjected to hypoxia. Moreover, a significant increase in **BNIP3** expression was detected in postnatal ventricular **myocytes** and adult rat hearts subjected to hypoxia. An increase in **BNIP3** expression was detected in adult rat hearts in vivo with chronic heart failure. Subcellular fractionation experiments indicated that endogenous **BNIP3** was integrated into the mitochondrial membranes during hypoxia. Adenovirus-mediated delivery of full-length **BNIP3** to **myocytes** was toxic and provoked an 8.3-fold increase (P<0.05) in **myocyte** death with features typical of apoptosis. Mitochondrial defects consistent with opening of the permeability transition pore (PT pore) were observed in cells expressing **BNIP3** but not in cells expressing **BNIP3** missing the carboxyl-terminal transmembrane domain (BNIP3DeltaTM), necessary for mitochondrial insertion. The pan-caspase inhibitor z-VAD-fmk (25 to 100 micromol/L) suppressed **BNIP3**-induced cell death of ventricular **myocytes** in a dose-dependent manner. Bongkrekic acid (50 micromol/L), an inhibitor of the PT pore, prevented **BNIP3**-induced mitochondrial defects and cell death. Expression of BNIP3DeltaTM suppressed the hypoxia-induced integration of the endogenous **BNIP3** protein and cell death of ventricular **myocytes**. To our knowledge, the data provide the first evidence for the involvement of **BNIP3** as an inducible factor that provokes mitochondrial defects and cell death of ventricular **myocytes** during hypoxia.

L6 ANSWER 3 OF 5 CA COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 139:334602 CA
TITLE: Antibody, antisense oligonucleotides and **mutant** NIP3 protein for modulating necrosis and for treating neurol. and cardiovascular diseases
INVENTOR(S): Greenberg, Arnold H.; Geiger, Jonathan D.; Kirshenbaum, Lorrie A.; Hellner, Faye
PATENT ASSIGNEE(S): Can.
SOURCE: U.S. Pat. Appl. Publ., 74 pp., Cont.-in-part of Appl. No. PCT/US01/21043.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| US 2003203867 | A1 | 20031030 | US 2002-290461 | 20021108 |
| WO 2002002743 | A2 | 20020110 | WO 2001-US21043 | 20010629 <-- |
| WO 2002002743 | A3 | 20020516 | | |

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

| PRIORITY APPLN. INFO.: | | | |
|---|---|---|---|
| US 2000-215643P | P | 20000630 | |
| US 2000-219554P | P | 20000720 | |
| WO 2001-US21043 | A2 | 20010629 | |
| US 2001-348135P | P | 20011109 | |
| US 2001-344196P | P | 20011228 | |

AB Methods and compns. for modulating necrosis and for treating neurol. and cardiovascular diseases are described. The inventors have shown that **BNIP3** is involved in cell necrosis and cell death involved in cardiovascular and neurol. diseases. **BNIP3** was expressed and integrated into mitochondrial membranes. Broad spectrum caspase inhibitors Ac-zVAD-FMK and baculovirus p35 failed to inhibit **BNIP3** induced cell deaths. **BNIP3** did not activate caspases and **BNIP3** did not induce mitochondrial cytochrome c release. **BNIP3** induced cell death in the absence of a PAF-1, caspase-9, or caspase-3. **BNIP3** induced rapid plasma membrane permeability but not PE externalization. **BNIP3** induces the ultrastructural changes of necrosis. **BNIP3** mRNA and protein levels increased with excitotoxicity and glutamate increased **BNIP3** expression. **BNIP3** expression caused neuronal cell death and **BNIP3** -induced neuronal cell death in excitotoxicity required protein synthesis but was largely independent of caspase activity. Hypoxia induced expression of **BNIP3** in ventricular **myocytes** and hypoxia-induced mitochondrial integration of the endogenous **BNIP3** is suppressed by **BNIP3**ΔTM. **BNIP3** provoked widespread cell death of ventricular **myocytes**.

L6 ANSWER 4 OF 5 CA COPYRIGHT 2006 ACS on STN

| | |
|---|---|
| ACCESSION NUMBER: | 137:349637 CA |
| TITLE: | Hypoxia, BNip3 proteins, and the mitochondrial death pathway in cardiomyocytes |
| AUTHOR(S): | Crow, Michael T. |
| CORPORATE SOURCE: | Department of Medicine, Johns Hopkins University, Baltimore, MD, 21224, USA |
| SOURCE: | Circulation Research (**2002**), 91(3), 183-185 CODEN: CIRUAL; ISSN: 0009-7330 |
| PUBLISHER: | Lippincott Williams & Wilkins |
| DOCUMENT TYPE: | Journal; General Review |
| LANGUAGE: | English |

AB A review discusses the role of BNip3, a hypoxia-inducible member of the Bcl-2 family of the apoptotic regulators, in mediating cardiomyocyte cell death. BNip3 expression is significantly increased in response to hypoxia, enforced BNip3 expression causes cell death in normoxic cardiomyocytes, and enforced BNip3 **mutant** expression lacking its transmembrane domain partially blocks hypoxia-induced cell death. BNip3 play an essential role in the cellular response to hypoxia because its expression is regulated by the hypoxia-inducible factor transcription complex, its activity is tied to the Bcl-2 family of apoptosis regulators, and it is localized to the mitochondria, a site where numerous cell death regulatory pathways converge.

REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS